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EXAMINER	
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1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/673,038	GRIMM ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 10-14* is/are pending in the application.

4a) Of the above claim(s) *14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 10-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/21/2007 has been entered.

Claims Status

This action is in response to the papers filed on 11/21/2007. Currently claims 1-7 and 10-14 are pending.

Election/Restrictions

2. This application contains claim 14 drawn to an invention nonelected with traverse in the reply filed on 6/5/2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Objections

3. Claims 1-7 and 10-13 objected to because of the following informalities:

The claims 1-7 and 10-13 refers to table 1.

MPEP 2173.05(s) states:

Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is

no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-7 and 10-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting the presence of a TEM beta-lactam resistant micro-organism in a bacterial sample, said method comprising (i) obtaining a bacterial sample; (ii) isolating DNA contained in the sample; (iii) contacting the DNA of the sample with a micro-array, harboring on predetermined locations thereon different sets of capture probes, under conditions allowing hybridization of complementary strands, (a) wherein each representative of a set of capture probes comprises the sequence Rl-(X)-R2, wherein X consists of the nucleotide triplets of amino acid positions 2, 3, 4, 19, 37, 40, 49, 67, 78, 82, 90, 102, 113, 122, 125, 127, 143, 151, 161, 162, 163, 180, 182, 194, 202, 216, 235, 236, 237, 241, 258, 261, 264, 271, 272, 276, and 285 of the bla-TEM-1 gene and R1 consists of 25 consecutive nucleotides immediately 5' to X in the TEM1 and R2 consists of 25 consecutive nucleotides immediately 3' of X , (b) wherein the different sets of capture probes are selected such that an adjacent set starts at a given position 3n of nucleotides down-stream from the first set of capture probes, wherein n is an integer of 1 to 10, so that the

nucleotide sequence of the beta-lactamase gene is covered over a desired range, and (iv) determining if occurrence hybridization is indicative of(I) the presence of a TEM beta-lactam resistant micro-organism, does not reasonably provide enablement for a method of detecting the presence of "any" beta lactam resistant micro-organism in "any" biological sample and determining the particular polymorphism present in the TEM beta-lactam gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims broadly encompass a method of detecting the presence of a beta-lactam resistant micro-organism in a biological sample comprising: obtaining a biological sample, optionally isolating DNA from the sample, contacting the DNA of the sample with a microarray harboring at predetermined locations different sets of capture probes, under conditions that allow for hybridization of complementary strands, wherein each representative set of probes comprises a sequence R1-(X)-R2, which sequence represents a selected part of the sequence of a TEM beta lactamase exhibiting ESBL or IRT phenotype, wherein X represents a nucleotide triple of table 1 and R1 and R2 have a length of 3 to 20 nucleotides, wherein the different capture probes are selected such that an adjacent set starts 3n downstream from the first set and determining whether hybridization occurs and from the presence of hybridization and the location on the array is indicative of the presence of bet-lactam resistance and the genotype.

The claims thus broadly encompass detection of beta lactam resistance by the use of a microarray with probes comprising "any" triplet of nucleotides in table 1 with "any" length of nucleotides on either side of the triplet that are specific to "any" TEM beta lactamase gene.

Further this broadly encompasses detection of beta-lactam resistance by a probe with any codon recited in table 1 with any 3 nucleotides 3' of the codon and any 3 nucleotides 5' of the codon, as all naturally occurring nucleotides are specific to the TEM beta lactamse.

The claims further encompass the detection of beta lactam resistance by the presence of "any" hybridization to the array.

Further the claims encompass identification of the particular polymorphism for the location and presence of hybridization.

The amount of direction or guidance and the Presence and absence of working examples.

The specification teaches over 340 different beta-lactamase sequences have been identified (0002). The specification teaches that antibiotic resistance in ESBL- and IRT-enzymes are mainly due to 37 amino acid substitutions in 7 amino acid positions (0004). The specification further teaches that mutations resulting in IRT resistant are distinct from those leading to ESBL.

The specification further teaches that for any codon there are 64 permutations of nucleic acids (0030).

The specification teaches "The present invention also provides information about mutations having occurred in the beta-lactamse gene not yet know" (0033).

The specification further lists in Table 1, 88 codons of TEM beta lactamase (44 wildtype and 44 mutant by comparison to TEM-1).

The specification further teaches that 119 SNPs of the TEM beta lactamase were known at the time of filing (0051).

The specification further teaches 44 probes for known TEM beta lactamase (table 2). The specification teaches these probes represent most of the amino acid substitutions known at the time (0053).

The specification teaches in the example, "All the perfect match positions for blaTEM-1 could be identified correctly in every sample. The mean mismatch relative

intensities vary, most of them remain below 0.4, only S143, S161, S182, S276 show higher values up to 0.6. The standard deviation varies from 0.01 to 0.21. For most positions the [(MM or PM)/PM] ratio is reproducible <+/-10%. Only for Positions 127, 235, 236.2, 276 the variation is slightly higher, but the perfect match identification is without ambiguity" (0083). While the specification teaches hybridization of the sequence from the sample allowed identification without ambiguity of the perfect match sequences, it teaches that the mismatch sequences were not determined without ambiguity. As the specification teaches the mismatch sequences (mutant or antibiotic resistant) could not be identified without ambiguity it would not be able to predictably determine the particular polymorphism of the TEM beta-lactamase.

Further as the specification teaches that both the wildtype and mutant sequences hybridized to the array, it would be unpredictable to determine the presence of a beta-lactam resistant organism based on the hybridization.

The state of prior art and the predictability or unpredictability of the art:

Persson teaches hybridization of oligonucleotides is affected by length, temperature and complementarity (Analytical biochemistry (1997) 246 page 34-44) (see abstract). Persson teaches a fundamental problem in determining the sequence by by hybridization is to resolve ambiguities at due to mismatches at the terminal ends of the hybrids (see page 34, 2nd column, 1st full paragraph). Persson further teaches that addition of a single nucleotide can increase stability of a complex more than 10 fold (see page 41, 2nd column). Thus Persson teaches that hybridization assays are not

predictable at any probe length, temperature, percentage of complementarity, target length, or target concentration.

Draghici (Trends in Genetics (2006) volume 22, pages 101-109) teaches that increase the probe length from 25 to 30 nucleotides can increase senisitivity by 10 fold (see page 103, 1st column, 1st full paragraph) Draghici teaches that cross hybridization between probes that target the same region of a target sequence can result in unpredictable results (see page 107, 2nd column, last paragraph).

Kurkowa (Antimicorbial Agents and Chemotherapy (2003) volume 47, pages 2981-2983) teaches identification of a TEM-91 mutant that is resistant to ceftamizidime due to 3 mutations at codons 164, 184, and 240 (see abstract). Kurkow teaches that mutant has different kinetics than TEM 72 and TEM 5, TEM 46 and TEM 87 that have either the same mutations or mutations in amino acids that are proximal to codons 164, 184, 240. Kurkow thus teaches one could not predictably infer antibiotic resistance based on the presence of a mutant.

Ning et al (Nature Genetics 1996 volume 14, pages 86-89 and SCORE results) teach that SEQ ID NO 7 of the instant specification has 100% identity with GenBank Accession Z96537 GI:2181612 which is a human subtelomeric probe. Thus Ning et al teaches that sequences of the instant claims cannot be predictably associated with beta-lactam resistant microorganism, as the sequences are present in humans, which are not microrganisms. Thus performing the claimed method using the probes taught by the specification would identify a sample taken from a human as containing a TEM beta-lactam resistant sample. It thus is unpredictable.

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed, one would first have to establish that a predicative relationship exists between any nucleic acid sequence that comprises any of the codons recited in Table 1 and any 3 to 20 nucleotides to the 3' or 5' end codons, as all naturally occurring nucleotides specific to the TEM beta lactamase gene. This would be unpredictable as the claims broadly encompass every sequence in every genome, known or unknown. It would thus be unpredictable to associate hybridization to probes of any sequence with the presence of a beta lactam resistant antibiotic.

It would be unpredictable to associate the presence of any probe sequences taught in Table 2 of the specification with the presence of beta lactam resistance in a sample from a biological sample, as Ning in view of the SCORE alignment clearly demonstrates that SEQ ID NO 7 of the instant specification is identical to Accession Z96537 GI:2181612 which is a human subtelomeric probe. Thus hybridization of this probe would not predictably allow identification of microorganisms that are beta-lactam resistant, as SEQ ID No 7 would identify humans as a beta-lactam resistant microorganism.

Further it would be unpredictable to determine the presence of a particular polymorphism by hybridization as the specification teaches that mutant sequence could not be determined without ambiguity.

Further it would be unpredictable to identify the presence of beta-lactam resistant micro-organism with probes of different lengths, at different temperatures, with different target nucleic concentrations as Draghici and Persson teach that all of these factors alter the reproducibility and thus predictability of microarrays.

Due to the scope of the claims, one of skill in the art would be required to further undertake extensive trial and error experimentation.

Therefor, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

6. Claims 1-7 and 10-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims 1-7 and 10-13 encompass a method of detecting beta-lactam resistant bacteria based hybridization of probes of R1-X-R2, wherein X is "any" codon that is recited in Table 1, wherein R1 and R2 are any nucleotides that are specific to the beta lactamase gene. This broadly encompasses any nucleic acid that has a

codon that is specified in table 1, with any 3 to 20 nucleotides to the 3' and 5' as all natural occuring nucleotides are present in beta lactamase gene.

When the claims are analyzed in light of the specification, the invention encompasses an enormous number of nucleotide molecules. The specification teaches "The present invention also provides information about mutations having occurred in the beta-lactamase gene not yet know" (0033).

The specification further lists in Table 1, 88 codons of TEM beta lactamase (44 wildtype and 44 mutant by comparison to TEM-1).

The specification further teaches that 119 SNPs of the TEM beta lactamase were known at the time of filing (0051).

The probes thus encompass any nucleic acid sequence that comprises any of the codons recited in Table 1 and any 3 to 20 nucleotides to the 3' or 5' end codons, as all naturally occurring nucleotides specific to the TEM beta lactamase gene. Thus the claims broadly encompass every sequence in every genome, known or unknown.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been by full structure. The instant specification teaches 45 sequences, SEQ ID NO 1-45.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other nucleotide sequences or positions with in a specific gene or nucleic acid), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case the specification provides no structural or functional limitations. The

claims read in light of the specification encompass any nucleic acid molecule any nucleic acid from 9 to 43 nucleotides in length comprising any of the 88 codons recited in Table 1. This is an enormous genus of nucleic acids as probes of 9 nucleic acids in length have 4^6 possible permutations for the other 6 nucleotides not defined by the codons of table 1.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed probes regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a polymorphism, without any definition of the particular polymorphisms claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In

re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

In the instant application, the provided information regarding nucleic acid beta lactamase probes of formula R1-X-R2, do not constitute an adequate written description of the broad subject matter of the claims, and so one of skill in the art cannot envision the detailed chemical structure of the nucleic acids encompassed by the claimed probes. Adequate written description requires more than a statement that nucleic acids with a particular quality are part of the invention and reference to a potential method for their identification. The nucleic acid sequence is required.

In conclusion, the limited information provided regarding beta lactamase probes of formula R1-X-R2 is not deemed sufficient to reasonably convey to one skilled in the art nucleic acid molecules claimed.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-6, 8, 9, 11, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee, et al (Molecules and Cells (2002) volume 14, pages 192-197) in view of Blazquez, et al (Antimicrobial Agents and Chemotherapy (1995) volume 39, pages 145-149), Chee et al (A) (WO 95/11995), and Sutcliffe (Proceedings National Academy of Sciences USA (1978), volume 75 pages 3737-3741).

Claim 1 is drawn to obtaining a biological sample, optionally isolating DNA from the sample and contacting the DNA from the sample with an array with capture probes derived from the sequence of a beta-lactamase genes to determine the presence of a

beta lactamase resistant organism and mutations indicative of resistance to specific antibiotics.

With regards to claims 1, Lee teaches the use of arrays in which hybridization is indicative of beta-lactamase resistance (see abstract). Lee further teaches hybridization of target DNA with a DNA-chip, or micro-array, with probe sets at specific locations on the chip (see page 93 hybridization, preparation of DNA chip) to determine the presence of beta lactamase resistant genes (see figures 1, 3, 4) using probes of 21 nucleotides.

With regards to claims 2 and 3, Lee teaches isolation and amplification of target DNA from bacterial cells prior to contacting with array (see page 193, last paragraph 1st column and 1st paragraph 2nd column).

With regards to claims 8, Lee et al teaches a micro-array for the detection of various beta-lactamase resistant genes, including PSE, OXA, FOX, MEN, CMY, TEM, SHV, OXY, and *AmpC* (see abstract).

With regards to claim 11 and 13, Lee teaches the fluorescent labeling of DNA prior to contact with array (see page 193, column 1 last paragraph 3rd line up).

Lee et al does not teach a set of probes with all combinations of probes comprising R1- (X)-R2 of a beta lactamase gene (claim 1), fragmentation of DNA prior to contacting it with array (claim 4), beta-lactamases from Enterobacteriaceae (claim 5), or known SNPs in the beta-lactamase gene (claim 6).

However, with regards to claims 1,6, Blazquez et al teaches mutations, or SNPs, of beta-lactamase, including the mutation of gln39lys (specification refers to gln37lys)

(see figure 1) alter beta lactamase stability and antibiotic activity (see page 148 column 1, 1st 4 lines of next to last paragraph). (It is noted that there are two accepted number systems for beta-lactamases, the Ambler numbering system based used by Blazquez and the Sutcliffe system used in the specification. The two numbering systems may stem from Sutcliffe's sequencing pBR322 and Ambler sequencing the protein product of R6K (Proceedings National Academy of Sciences, USA (1978), Volume 75 pages 3732-3736). The art are normally presents mutants in reference to either Ambler or Sutcliffe numbering. The specification does not explicitly state a numbering system. Neither numbering system has glu at both codon 37 and 39. It is thus presumed codon 37 of specification and codon 39 of Blazquez are the same barring proof otherwise.) Blazquez further teaches introduction of known mutations into the TEM1 gene at codons 39, 104, 164, 237, 238, and 240 alter resistance of microorganisms to specific antibiotics (see table 2 and 3). Mutation of amino acid 39 specifically decreases the susceptibility to cephaloridine and ceftazidime, but not amoxicillin, amoxicillin plus cavulanic acid, cefotaxime, aztreonam, and meropenem (see tables 2 and 3, and page 146 2nd column paragraph (i).

With regards to claim 5, Blazquez teaches E.coli which is a member of the Enterobacteriaceae family.

With regards to claims 1and 4, Chee (A) et al teaches a tiling array (see Figure7 and page 37 line 10- page 38 line 34). Chee (A) teaches the use of immobilized arrays to interrogate a reference sequence and its codons with a target sequence for the identification of single base mutants in the reference sequence associated with disease

(see page 31 lines 6-7, and page 11 line 9 and 10). Further Chee (A) teaches this approach allows simultaneous detection and quantification of multiple target sequences (see page 32 lines18-19), allowing for sequence determination. The block-tiling array allows the interrogation of multiple nucleotide sites by use of multiple probe sets, which represent every permutation of nucleotides possible for a given nucleotide sequence. Chee (A) teaches the determination of all possible combinations of nucleotides surrounding a SNP using from 15-30 nucleotides (page 27 lines 2-6), allowing determination of all possible nucleic acid sequences. With regards to claim 4, Chee et al teaches DNA fragmentation (see page 126, number 4), prior to contacting with capture probes. Chee (A) teaches microfabricated arrays with large numbers of oligonucleotides offer great promise (see page 2 lines 11-13) for applications including identification of mutations related to disease, forensic studies, epidemiological and forensic studies. Chee (A) further teaches, "It is desirable to simultaneously diagnose the presence or absence of a variety of lethal common infections, determine the most effective therapeutic regime" (see page 64 lines 25-28).

With regards to claims 1 and 6, Sutcliffe teaches the nucleotide sequence of the beta- lactamase gene (see figure 3).

Therefore, it would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of identifying beta-lactamase resistance taught by Lee, to include identification of specific mutations resulting in resistance to specific antibiotics as taught by Blazquez with reasonable expectation of success. The ordinary artisan would be motivated to combine the teaching of Lee and

Blazquez in order to identify the specific beta lactam resistance present and provide proper treatment. It would have been further prima facie obvious to the ordinary artisan at the time the invention was made to improve the method of identifying specific mutations for specific resistance of Lee and Blazquez to incorporate a tiling array as taught by Chee (A) and use the beta lactamase sequence taught by Sutcliffe to allow simultaneous detection and quantification of multiple target sequences (see page 32 lines18-19), thus allowing thorough characterization of mutations known to alter beta lactam resistance, and possibly identify new mutations altering beta-lactam resistance . The ordinary artisan would be motivated to improve the method of Lee and Blazquez with the use of a tiling array as taught by Chee (A), because Chee (A) teaches simultaneously diagnose the presence or absence of a variety of lethal common infections, determine the most effective therapeutic regime (see page 64 lines 25-28). In performing the method of Lee, Blazquez, Chee (A), and Sutcliffe, the ordinary artisan would be motivated to specifically include a probe in the screening method, corresponding to the mutation at codon 37 (same as codon 39 taught by Blazquez), because Blazquez teaches that a mutation at this codon results in specific antibiotic resistance. The ordinary artisan would be motivated combine the teachings of Lee, Blazquez, Chee (A), and Sutcliffe to screen for the presence of mutations at codon 37 (codon 39 taught by Blazquez) with the use of tiling probes as taught by Chee (A) to detect the susceptibility to cephaloridine and ceftazidime. The ordinary artisan would therefore be motivated to construct a probe corresponding to mutations in codon 37, including a probe with the sequence of SEQ ID NO: 7 (claim 9), to provide tiling probes

with all possible combinations of nucleotides at codon 37. The artisan would have had a reasonable expectation of success using the known methods of array based nucleic acid hybridization, to detect known mutations by probes designed by known methods.

Response to Arguments

The response traverses the instant 103 rejection arguing that the references do not teach or suggest probes of the R1-X-R2 which represents a sequence selected from a beta lactamase gene representing ESBL or IRT resistance, wherein X is a triplet from table 1 and - R1 and R2 have a length from about 3 to 20 nucleotides. The argument has been thoroughly reviewed but is not found persuasive.

With respect to the arguments directed to probes of sequence R1-X-R2, the MPEP 2111.03 states, "The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps." Chee teaches an incremental succession of probes in a basic tiling strategy in which each probe differs from it predecessor by the acquisition of a 5' nucleotide and the loss of a 3' nucleotide as well as the nucleotide occupying the interrogation position (see page 11, lines 21-27 and figure 3). Chee teaches this tiling method allows for the detection of mutations or polymorphisms (see page 18, lines 8-10). Chee further teaches the use of probes are from 9 to 30 nucleotides, which is in the range of 9 to 43 nucleotides depicted by the formula R1-(X)-R2, in which R1 and R2 are each 3 to 20 nucleotides (see page 27, lines 4-5). Therefore Chee teaches a basic tiling array for detection of polymorphisms, which comprises the probe sets with a sequence of R1-X-R2.

The nucleotide sequence of the beta-lactamase gene taught by Sutcliffe (see Figure 3) would serve as the reference sequence for the incremental succession of probes taught by Chee, while mutations taught by Blazquez would direct the ordinary artisan to specifically examine triplets specifically known to result in beta lactam resistance. Further, the sequence taught by Sutcliffe is one permutation of the nucleic acid sequence, while the sequence in table 1 of Blazquez is another sequence resulting in beta lactamase resistance. The ordinary artisan would thus have the nucleotide sequence with the aligned amino acid sequence taught by Sutcliffe to readily determine the nucleic acids involved in each taught by Blazquez to result in beta lactam resistance use in Chee's method of tiling.

Response further asserts that the cited material fails to disclose or suggest using capture probes to detect the presence of a beta-lactam resistant micro-organism. This argument has been thoroughly reviewed but is not consider persuasive because Lee teaches, "a robust and fast DNA chip method was developed in order to detect the various beta-lactam antibiotic resistance in one slide" (see abstract). Thus Lee suggests or renders obvious detection of beta lactam resistant micro-organism by use of an array.

The response further asserts that one of ordinary skill in the art would not have reasonable expectation of success by combining the teachings of the cited art. First, MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be

supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." Here, the statements regarding reasonable expectation is an argument that has not supported by evidence.

Thus this rejection is maintained.

9. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lee, Blazquez, Chee (A) and Sutcliffe, as applied to claims 1-6, 8, 9, 11, and 13 above, in further view of Osano et al (Antimicrobial Agents and Chemotherapy (1994) volume 38, pages 71-78)

Claim 7 further limits the enterobacteriaceae beta lactamase of claim 5 to a serine or zinc beta-lactamase.

The teachings of Lee, Blazquez, Chee (A) and Sutcliffe are set forth above in pargraph 8. Lee, Blazquez, Chee (A), and Sutcliffe, do not teach on serine or zinc beta-lactamase from the bacterial family Enterobacteriaceae.

However, Osana et al, teaches S. marcescens is a member of enterobacteriaceae family (see page 76 column 1, lines 16-19). Osana further teaches class A and C beta-lactamases, including plasmid encoded TEM and SHV, are serine dependent (see page 71, column 1, lines 5 and 6 column 1 and column 2 lines 4-7). Osana further teaches class B beta-lactamases are zinc dependent (see page 71 column 2 lines 4-7). Osana teaches that some strains of the Enterobacteriaceae family

are reported to be resistant to imipenem therapy. Osana teaches IMP-1 a zinc beta lactamase confers imipenen resistance to S. marcescens and further demonstrates there is great variability in the amino acid sequence of known zinc beta-lactamases and suggests evolution independent of other known zinc beta lactamases (see figure 3).

Therefore it would have been prima facie obvious to the ordinary artisan at the time of the invention was made, to improve the method taught by Lee, Blazquez, Chee (A) and Sutcliffe, to include the zinc beta-lactamases as taught by Osano, et al for the purpose of detecting imipenem resistance in the Enterobacteriaceae family. The artisan would have a reasonable expectation of success as the combination would merely be using methods known to detect mutations in the prior art to detect known mutations in known nucleic acid sequences. The ordinary artisan would be motivated to use the method taught by Lee, Blazquez, Chee (A), and Sutcliffe to determine the presence of zinc beta lactamases in order to identify imipenen resistant strains, to allow for proper diagnosis and treatment.

Response to arguments

10. Applicant asserts in the reply filed 12/8/2006 for reasons discussed above that Chee, Sutcliffe, Lee and Blazquez do not meet the limitations of the independent claims and thus do not cure the defects of claim 7.

Applicant's arguments have been fully considered by they are not persuasive. The response asserts Claim 7 depends from Claim 5 and ultimately Claim 1. The response states that Lee, Blazquez and Chee (A) are discussed above and Osono does not cure the defects of the primary or secondary references. This argument is not

persuasive for the reasons presented above for Lee in view of Blazquez and Chee (A) and Sutcliffe. Lee, Blazquez, Chee , and Sutcliffe combine to teach each and every limitation of the claims from which claim 7 depends, further Osano teaches detection of zinc beta lactamases, thus Osana renders all of the the limitations of claim 7 obvious.

11. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lee, Blazquez, Chee (A), and Sutcliffe as applied to claims 1-6, 8, 9, 11, and 13, further in view of Chee (B) et al (Science (1996), Volume 274, pages 610-614) and Routier (Nucleic Acids Research, (1999) volume 27, pages 4160-4166).

The teachings of Lee, Blazquez, Chee (A) and Sutcliffe are set forth above. Lee, Blazquez, Chee (A), and Sutcliffe do not teach fragmentation of DNA to 15-50 nucleotides.

However, Chee (B) teaches fragmentation improves the uniformity and specificity of hybridization (see page 613 third column, lines 43 and 44). Routier teaches a method of fragmentation resulting in fragments of 15-50 nucleotides (see Figure 5).

Therefore it would be prima facie obvious for one of ordinary skill the art at the time of the invention to modify the method of Lee, Blazquez, Chee (A), and Sutcliffe for detection of beta lactamase resistance with the Routier method of DNA fragmentation wherein the fragments are 15-50 nucleotides. Routier teaches fragmentation with sizes of 15-50 nucleotides and Chee (B) teaches fragmentation improves uniformity and specificity of hybridization. The ordinary artisan would be motivated to optimize the size of fragments of the DNA prior to contacting with a microarray because Chee (B) teaches

it improves specificity and uniformity of hybridization. The artisan would have a reasonable expectation of success as Chee (B) teaches the use of fragmentation for microarray analysis as taught by the combination of. Lee, Blazquez, Chee (A), and Sutcliffe.

As stated in the MPEP, 2144.05 II, "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)."

Response to arguments

12. Applicant asserts in the reply filed 12/8/2006 for reasons discussed above that Chee, Sutcliffe, Lee and Blazquez do not meet the limitations of the independent claims and thus do not cure the defects of claim 10.

Applicant's arguments have been fully considered by they are not persuasive. The response asserts Claim 10 depends from Claim 4 and ultimately Claim 1. The response states that Lee, Blazquez and Chee (A) are discussed above and Chee (B) and Routier do not cure the defects of the primary or secondary references. This argument is not persuasive for the reasons presented above for Lee in view of Blazquez and Chee (A) and Sutcliffe. As Lee, Blazquez and Chee render the claims from which claim 10 depends and Routier teaches fragmentation, the instant rejection renders claim 10 obvious, as well.

13. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lee, Blazquez, Chee (A), and Sutcliffe as applied to claims 1-6, 8, 9, 11, and 13 above, and further in view of Behrensdorf, et al (Nucleic Acids Research (2002) volume 30, e64).

The teachings of Lee, Blazquez, Chee (A) and Sutcliffe are set forth above. Lee, Blazquez, Chee (A) and Sutcliffe do not teach labeling of DNA following contacting DNA with array.

However, Behrensdorf, et al teaches the detection of SNPs by binding fluorescently labeled mutS to mismatched DNA for detection of SNPs (see figure 1) on an array. Behrensdorf teaches this method allows, "robust detection of genetic variation," while decreasing hybridization times and shortening assay duration (see page 5, 1st column lines 1 and 2, and 2nd column lines 10-12).

Therefore it would be prima facie obvious to the ordinary artisan at the time the invention was made to improve the array based method of detecting the presence of beta-lactam resistant bacteria of Lee, Blazquez, Chee (A) and Sutcliffe by using fluorescently labeled mutS taught by Behrensdorf to label the DNA after contacting with array, because Behrensdorf teaches that it gives robust detection of genetic variations, decreases hybridization times and shorten assay duration. The ordinary artisan would be motivated to use the labeling method of Behrensdorf in the method of Lee, Blazquez, Chee (A) and Sutcliffe because Behrensdorf teaches that it gives robust detection of genetic variations, decreases hybridization times and shorten assay duration. The artisan would have a reasonable expectation of success as combining known methods for detecting nucleic acid mutations in an art accepted manner.

Response to arguments

14. Applicant asserts in the reply filed 12/8/2006 for reasons discussed above that Chee, Sutcliffe, Lee and Blazquez do not meet the limitations of the independent claims and thus do not cure the defects of claim 12.

Applicant's arguments have been fully considered by they are not persuasive. The response asserts Claim 12 depends from Claim 1. The response states that Lee, Blazquez and Chee (A) are discussed above and Behrensdorf does not cure the defects of the primary or secondary references. This argument is not persuasive for the reasons presented above for Lee in view of Blazquez and Chee (A) and Sutcliffe. The teachings of Lee, Blazquez and Chee render the claim 1 obvious, thus as Behrensdorf teaches labeling after the contacting the sample nucleic acids to an array, the claim 12 is also obvious.

Summary

No claims are allowed over prior art cited.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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